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It is Not a Bronchial Asthma

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Abstract

Bronchial asthma is a common chronic respiratory disorder greatly depending on history and clinical evaluation for diagnosis. In our daily practice many conditions can mimic bronchial asthma and misdiagnosed as asthma either for insufficient evaluation of the patient or great similarity in presentation with lack of specific or pathognomonic investigation. In this article we will discuss in brief some of these asthma similarities that we face in our daily practice.

Keywords: *Bronchial asthma, mimics, misdiagnosis.*

Abbreviations

BA: Bronchial asthma, BNP: Brain Natriuretic Peptide, CHF: Congestive Heart Failure, COPD Chronic Obstructive Lung Disease, CT: Computerized Tomography ECHO: Electrocardiogram, FEV1: Forced Expiratory Volume in 1 second, GERD: Gastro-esophageal Reflux Disease, GINA: Global Initiative for Asthma, MRI: Magnetic Resonance Irradiation, NIPPV: Non Invasive Positive Pressure Ventilation, PNDS: Post Nasal Drip Syndrome, PVFM: Paradoxical Vocal Fold Motion, RADS: Reactive Air way Dysfunction Syndrome, TBM: Tracheobronchomalacia, TM: Tracheomalacia, UAWRS: Upper Air Way Reactive Syndrome, VCD: Vocal cord dysfunction.

Introduction

Asthma, a heterogeneous syndrome, is a chronic inflammatory disease of the airways characterized by airway hyper-responsivenes to a variety of stimuli, resulting in reversible airflow limitation [1]. Being a heterogeneous disease together with many endotypes and phenotypes bronchial asthma include many varieties as cough variant asthma, exercise induced asthma, aspirin induced asthma... etc [2].

Although it is mainly a clinical diagnosis based on recurrent attacks of dyspnoea, wheezing, chest tightness and/or cough, the presence of these symptoms is not specific for bronchial asthma because similar symptoms can be present with other respiratory or even cardiac diseases, or may be triggered by different stimuli in non asthmatics (asthma mimics) as gastro esophageal reflux disease, vocal cord dysfunction, post nasal drip etc. These asthma mimics commonly treated as bronchial asthma resulting in resources exhaustion, over estimation of bronchial asthma, over estimation of resistant bronchial asthma and many side effects of improperly used asthma medications with social and financial problems for these patients [3,4].

A high index of suspicion for alternative diagnoses should be considered after evaluating a patient for bronchial asthma who presents with atypical symptoms or fails to respond to bronchial asthma therapy [4].

Postnasal Drip Syndrome (PNDS)

Known also as upper airway cough syndrome [5], was mentioned for the 1st time by Frank in 1794 in Latin article as a form of chronic catarrh the seat of which is the pharynx [6]. Although there is no acceptable definition for it [5], the most accepted one is a sense of fullness deeply seated in the back of the nose, with constant stinging and tickling sensation about the uvula, soft palate and posterior part of the hard palate that is aggravated after sleep [7].

The mechanism of cough in PNDS is direct irritation or inflammation of the cough receptors in the upper airway [8]. There is usually repeated episodes of colds and flu leaving the patient with a persistent condition of catarrh and change in mucociliary clearance with accumulation of mucus in the postnasal space [7] but it can be result from a number of different conditions that upset the normal production of mucus from the nasal and sinus cavities as allergic rhinitis, sinusitis, polyps, anatomical anomalies, gastro-esophageal reflux and smoking [9].

Because PNDS does not have any pathognomonic finding [10], the diagnosis is usually based on a careful detailed history that is usually contain an upper respiratory illness (e.g. cold) but also can be diagnosed strangely as a condition that responds to combination therapy of first generation antihistamine and oral decongestant [11]. Patient may suffered from a shorttickling cough occurring at intervals especially night and morning, frequent Diagnosis largely based on direct laryngoscope ideally after a bronchohawking and spitting of small viscid pellets of mucus [7,10].

After persistence of the symptoms for a period the voice becomes affected either from the constant presence of obstruction in the post-nasal space preventing the perfect approximation of the palate to the posterior wall or because the velum becomes actually week in its movements causing a tendency to speak through the nose [13].

Although inflammation, ulceration or swelling of the larynx may be not detected, shreds of stringy may be seen hanging down from behind the velum or the back of the pharynx and sometimes the mucus follicles are enlarged and red with cobblestone appearance of the oropharyngeal mucosa. Chest examination may be normal but wheeze is also common [7, 11, 12].

The treatments of PNDS include nasal washing with mild alkaline solutions containing borate [14], first generation antihistamine and oral decongestant as recommended by American chest colleague physician [12] then all efforts are directed to treat the underlying condition aiming to resolve the problem such as antibiotic therapy and functional endoscopic sinus surgery for treating sinusitis [9].

Vocal Cord Dysfunction (VCD)

Known also as paradoxical vocal fold motion (PVFM), is an abnormal adduction of the vocal cords during inspiration (less commonly during expiration) that produces airflow obstruction at the level of the larynx commonly among women and usually misdiagnosed as bronchial asthma not only due to similar presentation but also due to similar triggers of symptoms [14].

It is first described clinically in 1842 as a dysfunction of the laryngeal muscles that is seen in hysterical women [15] and was first visualized during laryngoscope in 1869 by Mackenzie who made the diagnosis in hysteric patients [16].

The exact cause of this condition is not clearly defined and may be multi-factorial [17] but the underlying pathophysiology involves a hyper functional and inappropriate laryngeal closure reflex triggered by exertions, psychological factors and irritants as GERD, laryngopharyngeal reflux, rhinitis, sinusitis, recurrent upper airway viral infections, environmental allergens and/or pollutants and occupational irritant fumes [18, 19, 20].

The clinical presentation is widely variable including air hunger, sensation of choking, chest tightness, chest pain, difficulty swallowing, globus sensation, hoarseness of voice, intermittent aphonia or dysphonia, neck or chest retractions, fatigue, cough, throat clearing and stridor which can induce fear, panic attack and anxiety with further worsen respiratory symptoms which is similar to asthma attack but the sudden onset and offset, poor response to bronchial asthma treatment, absent of hypoxemia during attack, hoarseness of voice or a phonia and absent of nocturnal awakening due to breathlessness can help to differentiate it from bronchial asthma [21, 22, 23].

Diagnosis largely based on direct laryngoscope ideally after a broncho- provocation challenge, the flow-volume loop obtained through spirometry or pulmonary function testing and impulse oscillometry but also C1 inhibitor and C4 levels should be evaluated for exclusion of hereditary angioedema in suspected cases [24].

While transnasalfiber-optic laryngoscopy during an acute attack is the gold standard for the diagnosis allowing direct visualization of the paradoxical adduction of the true vocal cords during inspiration with glottic chink along the posterior portion of the vocal cords (Figure 1), the flow-volume loops is a useful tool in differentiating VCD and BA which typically show inspiratory loop flattening (variable extra thoracic obstruction) in VCD (Figure 2) in addition to an abrupt drop and rise in the expiratory flow volume loop in the absence of coughing during vocal cord dysfunction symptoms [22, 25].

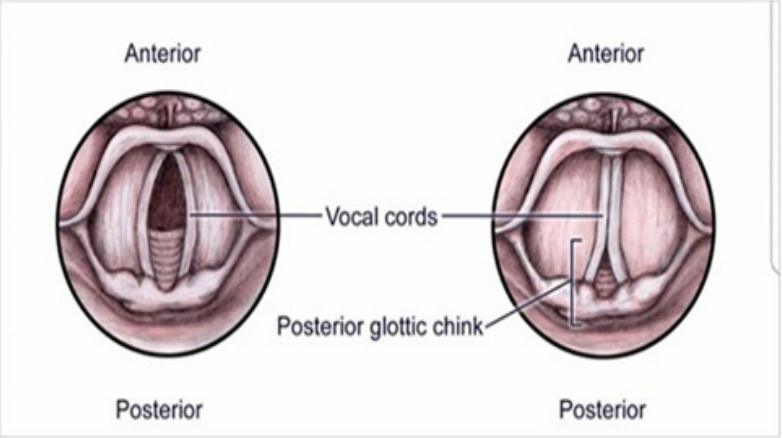

Fig 1. *Vocal cord during normal inspiration left and in patient with vocal cord dysfunction right.*

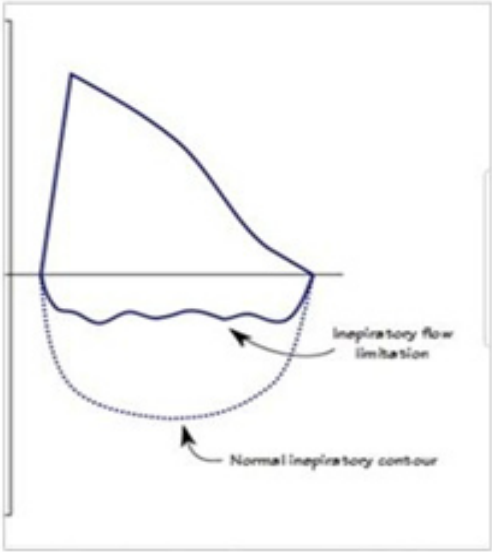

Fig 2. *Spirometry in patient with vocal cord dysfunction showing inspiratory flattening.*

Management often requires a multidisciplinary approach involving the primary care physician, pulmonologist, allergist, otolaryngologist, gastroenterologist, neurologist, psychiatrist or psychologist, speech pathologist and athletic trainer [26] with the mainstays of treatment is vocal cord relaxation techniques and breathing exercises with psychological support in difficult cases but neither diet restrictions are necessary nor specific pharmacotherapy is indicated [17-22].

Cardiac Asthma

Cardiac asthma is the presentation of congestive heart failure (CHF) with wheezing beside other symptoms as dyspnea, cough, frothy or bloody sputum and rales. These symptoms usually occur at night (but also may following exertion) and are more prevalent in the elderly population 35% versus 10% to 15% in younger patients [27, 28].

It is 1st published in 1833 by James Hope as inadequate oxygenation of blood with sense of suffocation [29]. In 1951, Lombardo and Harrison defined cardiac asthma as a condition induced by acute passive congestion and edema of the lungs when the left side of the heart "suffers from a sudden disproportion between work load and work capacity" [30].

About 10% of the population over the age of 80 years have heart failure [31] and about 10% of cases of dyspnea referred to a pulmonary specialist may have a cardiac cause rather than pulmonary cause [32].

In CHF, inability of heart to pump blood out of the left ventricle results in accumulation of fluid in the pulmonary circulation with pulmonary congestion which cause the inspiratory and expiratory difficulty with asthma like symptoms [33].

Cardiac asthma is often characterized by abrupt waking from sleep with dyspnea and wheezes which generally subside after the patient sits upright for 20 to 30 minutes and then patient may be able to return to bed without medication. However, patient may developed recurrent episodes in a single night with cyanosis, cold sweats, blood-tinged sputum, and fluid buildup in the lungs [30-34].

Wheezes experienced in patients with CHF may be due to a narrowing or obstruction of the bronchioles, bronchial hyper-reactivity [35], down regulation of beta2 receptors resulting from excessive adrenergic stimulation [36] or reflex bronchoconstriction involving the vagus nerve [37].

Because of sharing the similar symptoms and timing of BA, cardiac asthma is often misdiagnosed as BA. However, an accurate diagnosis is essential as treatments is different for the two conditions and incorrect treatment can exacerbate cardiac asthma [38].

While the absence of inflammation is the major difference between cardiac asthma and bronchial asthma, circulation time which is prolonged in heart failure patients and can be estimated by radionuclide angiocardiography CT and MRI can also differentiate between both conditions [39]. Measuring the serum Brain Natriuretic peptide (BNP) can also differentiate cardiac and pulmonary causes of dyspnea as it is increased in heart failure [40].

While chronic heart failure often is associated with decreased forced expiratory volume in 1 second (FEV1), cardiac asthma patients exhibited lower FEV1 values than patients with chronic heart failure alone [41].

Bronchial hyper-reactivity, the hallmark of BA, can be present in some degree in some patients with left ventricular failure [42] and diuretics are ineffective in altering this bronchial hyper-reactivity, suggesting that leftventricular failure can cause chronic changes to the airways [43].

Chest x-ray is a useful tool for confirming the presence of pulmonary congestion as well as for identifying cardiomegaly in cardiac asthma [37] and on examination, the lung auscultation may reveal rales [44].

Currently, no well-defined treatment for cardiac asthma in the acute or chronic setting and treatment of cardiac asthma depend on improving the pump function of the heart. While BA medications like bronchodilators and corticosteroid usually are ineffective in treating cardiac asthma, ipratropium bromide, an inhaled anticholinergic bronchodilator, may improve pulmonary function in patients with CHF and steroids may be clearly helpful for patient with pulmonary edema and significant wheezing that fails to resolve with the initial therapy [45].

Traditional medications used in the acute treatment of cardiac asthma include furosemide, morphine and nitrates [46-47]. Supplemental oxygen, noninvasive ventilation (NIV) and proper positioning of the patient also are important [47]. Proper positioning, in which the patient stands erect or sits upright with feet hanging off the side of the bed, will result in decreased venous return [48] with decreased the amount of blood to the bronchioles and reduced interstitial edema [30-48].

Persistent pulmonary congestion despite aggressive diuresis may be a problem in some patients so an intravenous nitrate, venodilator, may be used in both hypertensive and normotensive patients as it will lessen the pressure in the left ventricle, thereby reducing pulmonary congestion [49]. Intravenous morphine may relieve symptoms in patients with pulmonary congestion via venodilation and reduction in preload allowing easier breathing and reduces a patient's anxiety level during the attack [50-52].

After resolving of the acute attack, heart failure therapy should be initiated or optimized to prevent further attacks using angiotension converting enzyme inhibitors and beta-blokers with diuretics to maintain euvolemia and prevent future attacks. Although digoxin not shown to reduce mortality, it may be used to improve congestive symptoms [50-52].

Reactive Airways Dysfunction Syndrome (RADS):

Known also as upper air way reactive syndrome (UAWRS), is a controversial and poorly understood condition in which a sudden onset of asthma-like symptoms after a single exposure to a high concentration of irritant agents followed by asthma-like symptoms and airway hyper-responsiveness that may persist for a prolonged period [53].

It is 1st described in 1981 by Brooks and Lockers as a non-immunological asthma resulting from exposure to an irritant gas [54] that is differs from occupational asthma, because it is an acute single event without a significant latency period [55].

The symptoms, which mimic asthma symptoms, usually manifest within 24 hours of exposure although a few patients report symptoms after up to seven days of the exposure [56]. Patient may develop burning sensationin the throat and nose [57] in addition to cough, dyspnea, wheeze and chest pain [58] with symptoms of nasal mucosal irritation such as nasal congestion, sneezing, nasal pruritis and or increased nasal secretions [59]. Physical examination findings include conjunctivitis, pharyngeal erythema, tachypnea and wheezing [60].

The pathology of RADS shows nonspecific inflammation with cellular infiltration primarily lymphocytic and epithelial desquamation [61]. This inflammatory state with the toxic mediators causes epithelial injury. Although most people recover, extensive inflammation and epithelial sloughing could reduce receptor thresholds for severe ongoing bronchial hyper-reactivity [53].

While there is a list of recognized causal agents (table 1)the, most commonly reported agents in the literature associated with a diagnosis of RADS are chlorine, toluene diisocyanate and oxides of nitrogen [62].

The criteria for the diagnosis of RADS include documented absence of preceding respiratory complaint, exposure to very high concentration of irritant properties onset of symptoms within 24 hours after single exposure (but may delayed up to seven days), persistence for at least 3 months of asthma like symptoms, presence of airflow obstruction on pulmonary function ± nonspecific bronchial hyper-responsiveness and all other pulmonary disease were excluded [63].

A chest radiograph may be obtained to exclude non-cardiogenic pulmonary edema, alveolitis or pneumonia in patients presenting after an acute irritant exposure. High resolution computed tomography usually is not required for the evaluation of RADS but may be needed to exclude alternative diagnosesand may show evidence of air-trapping based on a mosaic pattern in the end expiratory images [64].

Agent	Examples
Household exposure	floor sealants, spray paint, bleaching agents, household cleaners containing morpholine.
Chemical	chlorine, sulphuric acid, ammonia, hydrochloric acid, acetic acid, phosgene, hydrogen sulphide, sodium azide, sodium hypochlorite, toluene di-isocyanates, organic solvents.
Industry	paint spraying, metal-coat removers, welding, heated plastics or acids, epoxy resins, perfumes, pesticides, enzymes, industrial cleaning products, dust or molds in silos.
Other	Fire and smoke inhalation, burning paint fumes, tear gas, locomotive exhaust

Table 1. *Causative agents of reactive air way dysfunction syndrome.*

For patients with chronic symptoms either allergy skin testing or immunoassay to a panel of common aeroallergens may be done to exclude allergic asthma [65].

Spirometry should be obtained in all patients suspected to have RADS with bronchodilator reversibility if airflow limitation is present. While obstructive pattern is the role with less response to a bronchodilator than in asthma [66] some patients show a restrictive defect [67].

While patient with RADS less responsive to Beta2 agonist than asthmatic patient, the treatment is the same as that of BA [68]. Systemic glucocorticoids is used in acute reactive airways dysfunction typically oral prednisone 40-60 mg for 10 to 15 days, which is longer than that used for typical exacerbations of bronchial asthma [69].

Nebulized sodium bicarbonate may improve quality of life and forced expiratory volume in 1 second (FEV1) after chlorine gas exposure [70] and lung transplantation has been used for severe ongoing symptoms of reactive air ways dysfunction syndrome [71].

Unlike immunologic occupational asthma, patient with RADS can return to their working environment with proper asthma treatment as long as their asthma is well-controlled and safety measures are taken to avoid high-level exposures [72].

The long-term outcome of RADS is unclear but the more concentration of offending agents associated with more high risk also vapours and wet aerosols more risky than dry particles [73].

Gastro Esophageal Reflux Disease (GERD)

Gastro esophageal reflux disease is the most common disease encountered by the gastroenterologist and defined as symptoms or complications resulting from the reflux of gastric contents into the esophagus, oral cavity and /or the lung [74].

Symptoms typically include dyspepsia, epigastric pain, nausea, bloating, early satiety and belching [74]. Chronic cough, asthma symptoms and chronic laryngitis may be also the presenting symptoms [75].

Gastroesophageal reflux have a complex relationship with bronchial asthma as at the time that both conditions can coexist together either one of them can induce the other or exacerbate it [75-77].

Gastroesophageal reflux may induce asthma symptoms either by direct effects on airway hyper-responsiveness or via increases in airway inflammation [7778]. Microaspiration of acid is a very potent direct stimulus for bronchospasm [78] and may trigger bronchospasm indirectly by the inflammatory changes which is either chronic localized inflammation with subsequently increased airway reactivity [77] or from released cytokines as a result of injury of the epithelial lining of the upper airway [79].

Also instillation of acid in the esophagus has been shown to decrease peak expiratory flow rates and increase overall airway resistance [80].

Asthmatic patients have a much greater prevalence of GERD symptoms than the general population [81]. Hyperinflation and descent of the diaphragm in bronchial asthma with increased work of breathing increases the pressure gradient between the abdomen and chest causing herniaion of the lower esophageal sphincter into the chest where its barrier function is impaired allowing more reflux of gastric contents [76]. Also asthma medications as beta2-agonists and theophylline may decrease lower esophageal sphincter tone which cause vicious cycle of GERD-induced asthma symptoms resulting in increased use of bronchodilators, which in turn promotes more GERD [82].

Treatment of GERD has variable effect on asthmatic patients while some patients with BA get benefits from GERD treatment with more symptoms control, some report no any benefits [83-84]. For this some recommend with an empiric trial of GERD therapy in poorly controlled asthmatics even if they do not have GERD symptoms [85] and others recommend against [86] and this again show the complex relation between GERD and asthma.

Tracheomalacia and Tracheobronchomalacia

Tracheomalacia (TM) is a weakness of the tracheal wall (mostly intra thoracic part) due to softening of the supporting cartilage and hypotonia of the myoelastic elements [87] resulted in narrowing of its lumen during expiration (specially forced expiration) with excessive dynamic airway collapse [88-89]. Tracheobronchomalacia (TBM), a more broad term, is diffuse or segmental tracheal and bronchial walls weakness and frequently used interchangeably with tracheomalacia [87-90].

While the signs and symptoms of TBM are non specific and similar to those of bronchial asthma, it is characteristically presented by barking cough, dyspnoea, stridor, wheezing, difficulty clearing secretions, recurrent bronchitis or pneumonia and syncope during coughing [91-92] but in mild obstruction may be asymptomatic [93]. These symptoms may be induced by forced expiration, cough, valsalva maneuver and certain clinical situations (eg: general anesthesia, progressive hypercapnic respiratory failure, liberation from mechanical ventilation) [94].

It can be classified in many ways one of them is according to shape of trachea and includes: crescent type in which there is anteroposterior tracheal narrowing, lateral type in which there is lateral tracheal narrowing with saber-sheath appearance and circumferential type in which there is both anteroposterior and lateral narrowing of trachea. Also commonly classified as congenital which is the most common trachea congenital abnormality and acquired which commonly faced after prolonged endotracheal intubation or tracheostomy [95-96].

The histopathological changes include narrowing of the lumen accompanied by atrophy of the longitudinal elastic fibers and fragmentation of the trachealcartilage [97] and can be classified into three histopathological types: the membranous type, the cartilaginous type and the polychondritic type [98].

Diagnostic tools include flexible bronchoscopy during which a decrease in the diameter of the trachea more than 50% is considered to be abnormal (Figure 3) [99-104], dynamic airway computed tomography (CT) and pulmonary function testing which can support the diagnosis, but are not diagnostic [100-102] although MRI is the preferred method for evaluating extrinsic airway abnormalities [103].

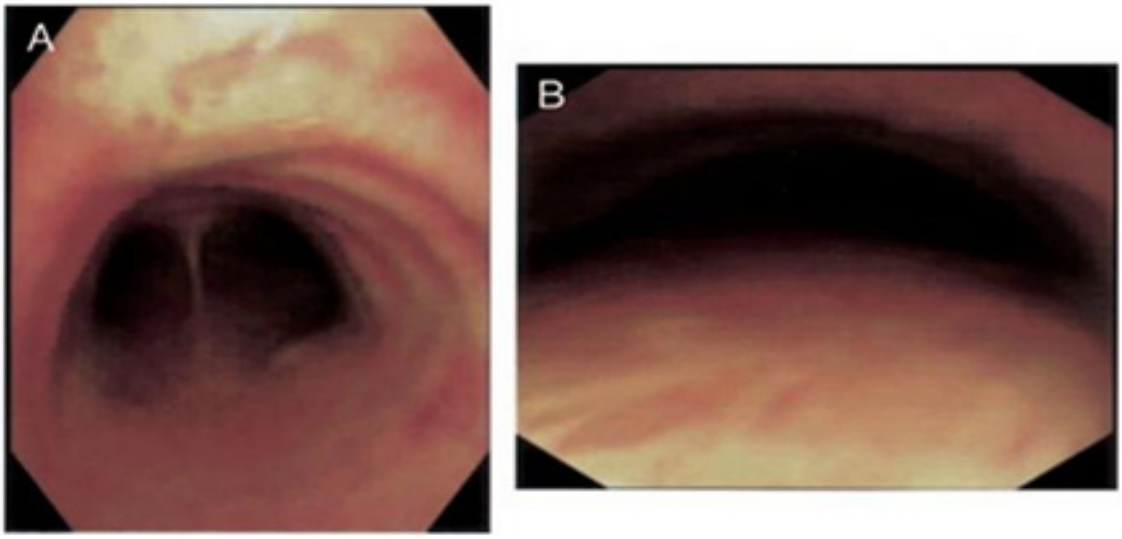

Fig 3. *Patient with Tracheomalacia*

A- Normal trachea during inhalation B- Trachea collapse during expiration.

Intervention is usually not necessary in children with mild-to-moderate TBM as the tracheal cartilage strengthens and stiffens with the child growth and symptoms resolved by age 1 or 2 years [105] so, conservative therapy is preferred (104) and includes the treatment of respiratory infections, humidified oxygen therapy and pulmonary physiotherapy [106]. Also asymptomatic adult patients generally do not require therapy, but for symptomatic patients the initial treatment targets the underlying cause and coexisting conditions [107].

Acting as a pneumatic stent, the non invasive positive pressure ventilation (NIPPV) can be used to maintain airway patency, facilitate secretions drainage and improve expiratory flow with reduction of the inspiratory transpulmonary pressures required to initiate airflow, therefore decreasing the work of breathing [108].

Airway stents can be used to restore and maintain airway patency with improvement of pulmonary function tests but more than one stent may be required [109].

Surgical intervention may be needed and includes: tracheal resection reconstruction that may be advised for patients with post-intubation and focal TM with satisfactory outcome [110], tracheal replacement and tracheobronchoplasty which refers to surgical splinting of the posterior wall of the trachea with polypropylene mesh [111].

Chronic Obstructive Pulmonary Disease (COPD)

COPD, a heterogeneous disease, is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and include: chronic bronchitis, emphysema and chronic remodeling bronchial asthma [112].

Although pathological changes of COPD are mainly in the airways, lung parenchyma and pulmonary vasculature are commonly affected with protease-anti-protease imbalance and oxidative stress are involved. Airways changes include chronic inflammation, increased numbers of goblet cells, mucus gland hyperplasia, fibrosis, narrowing and reduction in the number of small airways and airway collapse. These pathological changes result in increased resistance to airflow in the small conducting airways, increased compliance of the lungs, air trapping and progressive airflow obstruction [112-113].

Chronic inflammation in COPD is characterized by the presence of CD8+ T-lymphocytes, neutrophils and CD68+ monocytes/macrophages in the airways (114) while in bronchial of asthma, it is characterized by the presence of CD4+ T-lymphocytes, eosinophils and increased interleukin (IL)-4 and IL-5 [115].

Although cigarette smoking is clearly the single most important risk factor in the development of COPD, the prevalence is also related to outdoor, occupational and indoor pollution as biomass fuels use [116].

Dyspnea, chronic cough, and sputum production are the cardinal symptoms of COPD together with wheezing but, the most common early symptom is exertional dyspnea. These symptoms which is similar to those of BA may be developed independently and with variable intensity [118].

The diagnosis of COPD depends on the proper history and appropriate examination with an obstructive evidence provided by spirometry specially in current or former smoker aged more than 35 years. Chest x ray can exclude other diagnosis and may show hyper-inflation or emphysematous changes figure 4 but computerized tomography (CT) of chest clearly defined emphysema and it's extent. Also, ECHO can detect the affection of the right side of the heart with development of corpulmonale [119].

Although COPD has no cure due to the permanent damage to lungs, smoking cessation is the single most effective intervention in prevention and treatment together with pharmacological and non pharmacological measures. Pharmacological measures including mainly bronchodilators and inhaled steroids (in certain situations) with phosphdiestrase 4 inhibitor (Roflumilast) in contrast to BA in which inhaled steroids is the gold standard. Non pharmacological measures include oxygen therapy, pulmonary rehabilitation, immunization including influenza and pneumococcal vaccines, nutritional care, ventilatory support and surgical interventions including lung volume reduction surgery and lung transplantation [112-121].

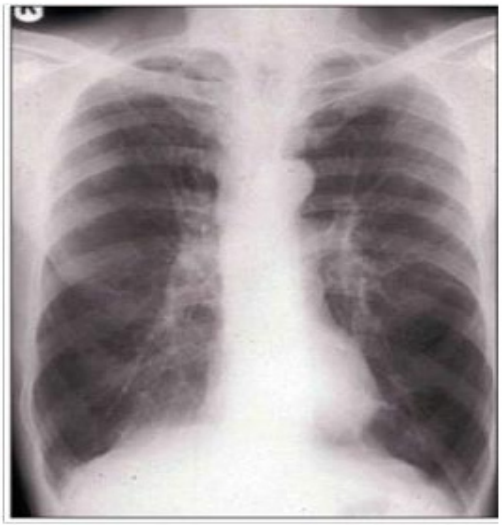

Fig 4. *Chest x ray in patient with COPD showing hyper-inflation with f lat diaphragm prominent pulmonary arteries and increased translucency of lung fields.*

Conclusion

As there is neither specific test for diagnosis nor pathognomic presentation of bronchial asthma with similarity of its symptoms to many other common clinical conditions, we should be extremely careful during evaluation of our patients with detail history taking and full proper examination and investigations considering always other possible diagnosis specially if there is a typical presentations or poor response to treatment taking in mind the coexisting of many conditions together.

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